FDA Cites Flaws in Hopkins Asthma Study

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The Johns Hopkins University medical researcher conducting an asthma study in which a young woman died last month failed to request federal permission before using an unapproved substance on study participants, according to a Food and Drug Administration document released yesterday.

Nor were research volunteers told that inhalation of hexamethonium constituted an experimental use of that chemical, a FDA investigator wrote, an omission that undercut the volunteers' ability to give effective informed consent.

Those preliminary findings, among five "inspectional observations" noted as the agency began its inquiry into Ellen Roche's death, center on the administration of hexamethonium to provoke airway constriction. One day after inhaling the substance during what was considered a relatively low-risk clinical trial, the 24-year-old laboratory technician began having breathing problems. She died several weeks later of acute respiratory distress, the first death of a Hopkins research subject in more than 15 years.

David Lepay, the FDA's senior adviser for clinical science, stressed yesterday afternoon that its probe is continuing and "is still very much an open investigation." He cautioned against drawing conclusions about the asthma study's apparent problems based on the initial Form 483 document.

But, he said, already it appears that several "control points" intended to ensure the safety of any clinical trial were compromised by asthma specialist Alkis Togias, the associate professor of medicine who was coordinating the study at the Hopkins Asthma and Allergy Center.

Not only did Togias fail to submit an IND -- for investigational new drug -- to the agency, but he also did not tell the university's institutional review board when he deviated from his stated protocol in how hexamethonium would be administered. In two cases, for example, he mixed it with sodium bicarbonate, though that did not necessarily increase any risk to those individuals.

Additionally, the review board was not informed when the first study subject developed a "persistent cough" two days after inhaling the substance. The cough lasted nine days, according to the FDA document, and yet Togias "failed to report [the] unanticipated adverse event."

The FDA and the federal Office for Human Research Protections are looking into Roche's death, as is a special review committee of Hopkins doctors and outside experts. The university has said that panel's report would be forwarded to federal officials by July 13.

The project was focusing on the physiological mechanics of a normal lung as a way of understanding why an asthmatic lung responds as it does to allergens and irritants. Nine healthy men and women had been recruited as volunteers, though only three had been given the hexamethonium when the research was halted after Roche became ill in early May.

The consent form that all signed should have included language describing the proposed use of hexamethonium

as experimental, Lepay said.Because it is not an approved drug, particularly for inhalation purposes, some of its risks are unknown and participants needed to understand that before deciding whether to sign on, he continued. "That is part of effective informed consent," he said.

For decades, hexamethonium was commonly taken for hypertension until it was pulled from the market because newer drugs became available. The two-page "clinical investigation consent form" that Roche signed described its risks as low blood pressure and dizziness.

In a written statement yesterday evening, Hopkins officials said Togias will provide its inspectors a written response within two weeks. But it responded point by point to the FDA's preliminary observations.

Although FDA officials maintain that their approval was required for use of hexamethonium, both Togias and the university's review board had concluded otherwise because the study was not testing "the therapeutic value" of what once was a commonly prescribed drug. "Since the event, the [review board] has placed a hold on investigations involving agents for which there is not an IND number until we consult with the FDA," the statement said.

It said that Togias did not report the first volunteer's cough because he thought it was "an upper respiratory ailment going around campus at that time." He altered the substance she and others were administered for the "comfort of the volunteers." On both points, Hopkins officials said, faculty members now have been reminded that the review board must be notified of any changes in research protocols and research participants' health status.

Finally, the statement detailed, the review board believed the study's consent form was "adequate in addressing known risks. This issue is being addressed by the internal review committee, and we are awaiting its findings."

Craig Schoenfeld, a Baltimore lawyer representing Roche's relatives, said the family was conducting its own investigation and probably would have no comment until that and the various federal inquiries are completed. He would not elaborate on the family's current course of action.